

Other Accomplishments

Principal Investigator: ALEXANDRE, LUCIEN

Grant Number: 5F31NS044583-03

Title: Minority Predoctoral Fellowship

Abstract: As I am in the very early stages of the MST program, I have yet to select a thesis laboratory or complete my laboratory rotations. However, I have identified several laboratories whose research interests parallel my own, i.e., studying the mechanisms behind and understanding the onset of neurodegeneration. One such laboratory with whom I completed a rotation this summer is embarking on a very exciting new direction in the study of neurodegenerative diseases as a function of early determination in neural stem cells rather than being an age related phenomenon. Dr. Mehler's studies are aimed at identifying which stage of development is instrumental for the commitment to the brain cell population that will undergo cell death later in life. These studies and the means for answering such revolutionary questions will encompass the latest in dissociated cell culture, molecular biology, and genetic analysis in order to identify the origins of diseases such as Alzheimers, Parkinson and Huntingtons diseases. Should these experiments prove fruitful this would provide a novel approach to our understanding of neurodegenerative diseases and open the gates to new treatments and screening for individuals early in life even before the onset of disease.-

Principal Investigator: ARNOLD, ARTHUR P

Grant Number: 5R01NS045966-02

Title: Sex Differences in Dopamine Systems

Abstract: The proposal has the long term goal of determining the factors that cause sex differences in structure, function, and susceptibility to disease in mesencephalic dopamine systems. The studies will investigate the cellular and molecular mechanisms by which sex chromosome genes induce sex differences in phenotype of dopaminergic neurons in vivo and in vitro. Studies will determine whether the sex chromosome effect is due to genes on the X or Y chromosomes; whether steroid hormones of the Sry gene participate in the induction of sex differences; when during development the sex chromosome effect occurs; whether the sex chromosome effect is direct or indirect on dopamine neurons; the cellular mechanisms of the sex chromosome effect; and whether the sex chromosomes contribute to sex differences in the development and adult structure of the nigrostriatal dopamine system in vivo. The proposed studies will contribute to an understanding of the principles of sexual differentiation of the brain. At issue are the molecular mechanisms by which male and female brains differ, which is relevant to the biological basis of abnormalities of sexual differentiation, and to the explanation of sex differences in neurological and psychiatric disease, not only of those that affect dopamine systems (e.g., Parkinson's Disease, Tardive Dyskinesia, Tourette's Syndrome, schizophrenia), but other sexually dimorphic diseases as well. (e.g., Multiple Sclerosis). Understanding sex differences in brain function will help develop sex-specific strategies for treatment of brain diseases.-

Principal Investigator: Biglan, Kevin M

Grant Number: 2L30NS050062-02

Title: Clinically Meaningful Outcomes in Parkinson's Disease

Abstract: Unavailable

Principal Investigator: BOYLAN, LAURA S

Grant Number: 1L30NS049909-01

Title: Emotion/Depression in Epilepsy & Parkinson's Disease

Abstract: Unavailable

Principal Investigator: DAUER, WILLIAM T

Grant Number: 1K02NS045798-01A1

Title: The mechanism of MPTP resistance in synuclein null mice.

Abstract: My long-held career goal is to investigate questions of importance to both patient care and fundamental biology. During medical training, I developed a strong interest in the basic pathogenic mechanisms of Parkinson's disease (PD), an illness characterized by degeneration of substantia nigra dopamine (DA) neurons and cytoplasmic aggregates of alpha-synuclein (SYN). I came to appreciate the power of genetically modified animals as tools to explore basic aspects of disease pathogenesis, and developed expertise in the generation of such animals. However, I now need to acquire skills necessary to assess the consequences of PD-related mutations on cellular and behavioral aspects of dopaminergic function in these animals. To accomplish this goal, I have developed collaborations with experts in PD research, and will pursue the proposed work within the integrated PD research group at Columbia University. Rarely, PD may be caused by missense mutations in SYN. However, normal SYN function and the mechanism by which pathogenic mutations disrupt SYN biology and lead to PD are poorly understood. MPTP-induced degeneration of DA neurons is a commonly studied model of PD. We find that SYN null mice display striking resistance to MPTP-induced degeneration of DA neurons, and this resistance appears to result from an inability of the toxin to access and inhibit its target, mitochondrial complex I. The goal of this research plan is to exploit this robust phenotype of SYN null mice to gain insight into the normal function of SYN, and explore how this function is altered by PD-causing mutations. In Aim 1 we will measure whether known concomitants of complex I inhibition (increased lactate and reactive oxygen species; decreased ATP) are also impaired in SYN null mice, and characterize processes that control access of the toxin to complex I (vesicular and monoamine transporter function). In Aim 2 we will further explore whether altered synaptic function underlies the MPTP resistance of SYN null mice by testing whether they are selectively resistant to toxins that traffic through the synapse. In Aim 3, by restoring wild type or mutant SYN to specific neuronal populations of SYN null mice, we will test whether the MPTP resistance is a cell autonomous phenomenon and whether pathogenic SYN mutations modify an aspect of its function involved in effecting MPTP-induced neurodegeneration. This proposal exemplifies the type of clinically related fundamental neurobiological research I plan to pursue during my career.-

Principal Investigator: DEBBURMAN, SHUBHIK

Grant Number: 1R15NS048508-01

Title: Yeast Model for Two Neurodegeneration-Linked Proteins

Abstract: Budding Yeast (*S. cerevisiae*) has emerged as a powerful model system for understanding molecular aspects of many human diseases. Protein misfolding linked to certain neurodegenerative diseases (NDDs) like Huntington Disease, Lou Gehrig's disease, and prion diseases have been successfully recapitulated in *S. cerevisiae* and led to identification of therapeutically relevant regulators of misfolding. No *S. cerevisiae* models for Parkinson's Disease (PD) or dentatorubral pallidoluysian atrophy (DRPLA) have been reported. PD is one of the most common NDDs, while DRPLA is a rare inherited NDD of the triplet repeat disease family. In both diseases, misfolding of a specific protein (alpha-synuclein for PD and atrophin for DRPLA) is thought to cause selective neuronal death. Unlike the well-characterized huntingtin protein in Huntington Disease (which shares many similarities to DRPLA), less is known about the misfolding of mutant atrophin in DRPLA. A *S. cerevisiae* expression system for studying alpha-synuclein has recently been developed in our lab. Preliminary evidence supports that both wildtype and disease-associated mutants are aggregating within yeast cells and upon purification. A similar effort to establish atrophin-1 expression in yeast is underway. To extend initial observations with alpha-synuclein in yeast and fully develop a yeast model for atrophin, three goals are proposed. 1) Misfolding properties between wildtype and mutant versions of both proteins will be investigated in vivo (immunofluorescence and GFP-based localization and assessment of protein half-life) and in vitro (by measuring protease sensitivity and differential solubility). 2) Influences of chaperones and ubiquitin-proteasomal pathway proteins on folding and degradation of these proteins will be assessed in strains compromised for chaperone/proteasomal function, or those that overexpress chaperones, and by co-immunoprecipitation assessment. 3) A fission yeast (*S. pombe*) expression model for alpha-synuclein and atrophin properties (as in Aim 1) will be developed and compared with the *S. cerevisiae* model; NDD models have not been reported in *S. pombe*. These studies may further clarify the molecular bases for misfolding and degradation of PD- and DRPLA-linked proteins and extend the usefulness of yeast models. Importantly, the scientific training of many undergraduates will be supported, strengthening their cell biology and molecular genetics skills and appreciation for model organisms. -

Principal Investigator: DUNAH, ANTHONE W

Grant Number: 1K01NS049006-01

Title: REGULATION OF NMDA RECEPTOR TRAFFICKING BY DOPAMINE

Abstract: This grant is a request for a NINDS Career Development Award for Minority Scholars in Neuroscience (K01) to investigate the Regulation of NMDA Receptor Trafficking by Dopamine. Interactions between the dopaminergic and glutamatergic systems in the striatum have implications for the pathogenesis and treatment of Parkinson's disease. My previous work has revealed significant modifications in the properties of striatal NMDA glutamate receptors in animal models of Parkinson's disease. Intriguingly, the alterations in striatal NMDA receptors occur at the level of assembly, phosphorylation and synaptic localization of the subunit proteins, and involved redistribution of receptors between sub-cellular compartments. Furthermore, we recently reported evidence for a rapid dopamine D1 receptor dependent mechanism for the trafficking of striatal NMDA receptors from intracellular compartments to the post-synaptic membrane. The molecular mechanisms for the dopamine D1 receptor mediated sub-cellular trafficking of NMDA receptors in the striatum remain largely unknown. Therefore, I will apply my molecular neuroscience and neuropharmacology backgrounds to experimentally explore and unravel the dopamine receptor dependent molecular mechanisms and signaling pathways underlying the trafficking of striatal NMDA glutamate receptors to brain synapses in primary cell culture system. As a research fellow, I have gained knowledge and received proper training in molecular mechanisms of dopamine and glutamate mediated signal transduction pathways in both in vivo and in vitro systems. The proposed career development program will further my understanding of how the dopamine and glutamate systems in the striatum interact and lead to the pathogenesis of Parkinson's disease. This career development program along with my assembled team of scientists will continue to contribute to my professional and intellectual growth, and eventually establish myself as an independent investigator. The findings from this research proposal may ultimately lead to the development of new therapeutic options for human Parkinson's disease.-

Principal Investigator: Goldstein, David

Grant Number: 5Z01NS002979-06

Title: Clinical Neurocardiology: Catecholamine Systems In Stress And Disease

Abstract: Unavailable

Principal Investigator: GROSS, ROBERT E

Grant Number: 1K08NS046322-01A1

Title: Axon Guidance Molecules in Nigrostriatal Regeneration

Abstract: We are interested in developing strategies for the reconstitution of the dopaminergic (DA) nigrostriatal (NS) pathway that degenerates in Parkinson's disease, an important goal because of the inadequacy of current long-term treatments. Attempts to reconstruct this pathway through transplantation of precursor cells or neurons into the nigra of the adult fail, likely as a result of 1) the presence of inhibitory molecules and/or 2) the absence of trophic and guidance molecules in the adult CNS. Here we propose that an understanding of the molecular events that regulate the development of the nigrostriatal pathway will provide insights for strategies designed to improve NS pathway regeneration in the adult milieu. We propose - and have exciting preliminary data to support - that axon guidance molecules (AGMs), important molecules that direct the development of other projection pathways in the CNS, are expressed in the developing DA NS pathway. A series of experiments are proposed to elucidate the role played by AGMs and their receptors in the development of the NS pathway. Our specific aims are to: 1) Define those AGMs whose receptors are expressed in the developing axons of nigral DA neurons; 2) Define the expression of AGM ligands in relation to the developing NS pathway; 3) For those AGMs that are expressed in an appropriate anatomical relationship to influence NS development, and whose receptors are expressed in developing DA neurons, directly demonstrate chemotropic effects on fetal nigral DA neurons in vitro, and their importance in the development of the NS pathway with blocking studies ex vivo. The outcome of the experiments outlined in this proposal will hopefully be the refinement of means to counteract the inhibitory milieu of the adult injured nervous system, and recapitulate the attractive and repulsive factors that direct axonal outgrowth during development, thereby paving the way for novel reconstructive and regenerative strategies to ameliorate the symptoms of Parkinson's disease. The insights derived from these studies may also have applicability in other neurodegenerative diseases, brain injury and stroke. The research outlined is part of a customized five-year plan of training and career development for the Principal Investigator. The proposal includes active mentoring by experienced scientists, access to diverse resources, and an environment uniquely suited to help the PI develop as an independent neurosurgeon-neuroscientist. -

Principal Investigator: HERSHEY, TAMARA G

Grant Number: 5K23NS041248-04

Title: Dopaminergic Modulation of Working Memory in PD

Abstract: The applicant is a clinical neuropsychologist with graduate training in neuropsychology and postdoctoral training in neuropharmacology and positron emission tomography (PET). The goal of this career development award is to integrate and advance these two areas of interest to answer questions about the neuropharmacological and neurophysiological basis of cognitive dysfunction in movement disorders such as Parkinson's disease (PD). This award will provide the applicant with training in the technical and theoretical issues related to using cognitive and pharmacological activation techniques in functional magnetic resonance imaging (fMRI). Long-term objectives are to address questions about the neural basis of cognitive dysfunction in movement disorders related to dopaminergic and/or basal ganglia dysfunction, such as PD, Tourette's syndrome and Huntington's disease. In addition, questions about the effects of dopaminergic treatments for these and other disorders (e.g. dystonia) on cognitive and neurophysiological functioning are also of interest. Cognitive dysfunction in these diseases, either due to the disease process itself or its treatments, can be limiting and disabling. Understanding the neurophysiologic basis for these symptoms may aid in assessing the effectiveness of current treatments or in developing better treatments. During the award period, the applicant will develop expertise in the use of fMRI, cognitive and neuropharmacological techniques to study these disorders, and will continue to hone her clinical skills in the neuropsychological assessment of movement disorders. The applicant will apply these new techniques to investigate the role of dopamine in working memory. The specific aims of the proposed studies are to test the hypothesis that 1) PD affects prefrontal cortex involvement in working memory and 2) dopaminergic modulation of working memory primarily occurs due to changes in lateral prefrontal cortical activity. To test these hypotheses, the applicant will first perform a behavioral study examining the effects of a steady-state infusion of levodopa, a dopamine precursor, on verbal and spatial working memory in PD patients and controls. The results of this study will then guide the choices of working memory tasks for an fMRI study. Subjects will be asked to perform working memory tasks before and during a steady-state infusion of levodopa. Modulation of the lateral prefrontal cortex is predicted during levodopa infusion. The degree of modulation is predicted to depend on baseline dopaminergic status (PD vs control) and the degree of memory load (low vs high). -

Principal Investigator: HOLLOWAY, ROBERT G

Grant Number: 5K24NS042098-04

Title: Neurology Outcomes Research: Clinical Trials/ Training

Abstract: New insights into the pathogenesis of Parkinson's disease (PD), the availability of a wider array of anti-parkinsonian therapies, the evolution of better tools for evaluating and monitoring disease progression have combined to change the current management of PD and the future landscape of PD-related therapeutic clinical trials. This proposal outlines the key initial steps to develop the clinical trial methodology that allows for the long-term assessment of quality of life and economic outcomes in chronic neurological conditions. This will be accomplished by extending the duration of large multicenter clinical trial of pramipexole versus levodopa in early PD and augmenting the data collection effort to include clinical, quality of life, economic, and functional imaging outcomes. This will address questions for patients and providers on the best approach to treating early PD, as well as to provide a multidisciplinary research platform (clinical trials, quality of life assessment, and economic evaluation) to train a growing number of physician faculty and fellows at the University of Rochester in the theoretical, methodological, and practical knowledge and skills for a productive career in patient-oriented research. Dr. Holloway's position within the Departments of Neurology and Community and Preventive Medicine, and the Rochester Clinical Research Curriculum will ensure the recruitment of highly qualified trainees. -

Principal Investigator: HORTOBAGYI, TIBOR

Grant Number: 1R13NS047105-01

Title: International Symposium on Motor Control Using TMS

Abstract: This application is a single-year request of support for an international symposium, "Mechanisms of Movement and Sensation Using Transcranial Magnetic Stimulation" (TMS) as part of the XVth biennial Congress of the International Society of Electrophysiology and Kinesiology (ISEK), Boston, June 18-21, 2004. The rationale for the symposium is that in this era of specialization, research subdisciplines on the one hand and basic researchers and therapists on the other, tend to separate. This symposium is an effort to minimize this separation. The symposium's aim is to generate a novel synthesis of basic science and clinical mechanisms of motor cortex plasticity and thus facilitate the design of rehabilitation programs. Pascual-Leone, co-chair, (US), will provide a historical perspective on TMS and rTMS. Valero-Cabre (US) will discuss the effects of TMS and rTMS on the basic electrophysiological and metabolic properties of cortical neurons with reference to Parkinson's disease. Hortobagyi (US) will discuss the contralateral organization of the human nervous system. Taylor (Australia) will address the mechanisms of central fatigue in polio and chronic fatigue syndrome. Sawaki (US) will present on training-dependent plasticity of the motor cortex as evidence for short-term motor memory, specifically in stroke. Rothwell (UK) will address the effect of afferent input on motor cortex organization and plasticity in healthy subjects and in patients with dystonia and hand cramps. Manto (Belgium) as co-chair will moderate the discussions. The symposium will provide maximal interaction between speakers and attendees as it will take place in a plenary session format as the only ongoing session. Through student discounts, it will provide an economical opportunity for biomedical trainees to attend. The presentations will be published in IEEE Engineering in Medicine and Biology, making a substantial impact on the field by attracting the interest of neurologists, clinical neurophysiologists, basic and clinical movement and sensation neuroscientists, physical therapists, biomechanists, biomedical engineering researchers, roboticists, educators and students from the US and abroad.-

Principal Investigator: HUNG, ALBERT Y

Grant Number: 5K08NS041411-04

Title: Activity-Dependent Regulation of Synapses by Shank

Abstract: The goal of this project is to investigate the role of a newly discovered postsynaptic protein, Shank, in the regulation of dendritic spine morphology and cytoskeleton. Local electrical stimulation induces growth of dendritic spines, suggesting that synaptic activity directly modulates neuronal architecture and circuitry. The molecular basis for these activity-dependent changes is not known, but probably involves postsynaptic proteins that interact with receptors and/or cytoskeletal elements. Shank acts as a putative scaffold for multiple glutamate receptor subtypes and also binds to the actin-binding protein cortactin, which has been implicated in dynamic cytoskeletal rearrangement and translocates to synapses in response to glutamate. This study examines the role of Shank in the regulation of dendritic spines and its *in vivo* function through three specific aims. First a combination of cell biological, biochemical, and dominant inhibitory approaches will be used to determine the mechanism for glutamate-regulated cortactin translocation to synapses, and to identify if Shank-cortactin interaction is required for this response. Second, how Shank induces spine growth will be studied by structure-function analysis. Finally, a genetic approach, generation of a Shank1 "knockout" mouse, will be used to investigate the role of Shank proteins in brain development, in postsynaptic receptor organization, and in learning and memory. The long-term goal of the candidate is to understand how aberrant synaptic transmission contributes to neurologic disease. Synapses are the signal processing units of the brain, and overexcitation of synapses by glutamate is thought to play a role in both acute neuronal injury (such as stroke and seizure) and chronic neurodegenerative conditions (including Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis). Understanding how postsynaptic proteins, such as Shank, regulate activity-dependent synaptic plasticity may shed light on mechanisms of glutamate toxicity. The immediate goal is to obtain training in the most up-to-date techniques in molecular genetics, protein biochemistry, and cellular neurobiology, sponsored by Dr. Morgan Sheng, which will enable him to become a productive, independent molecular neurologist. -

Principal Investigator: KOPIN, ALAN S

Grant Number: 5R21NS043692-02

Title: Evaluation dopamine receptors in Parkinson's

Abstract: Parkinson's disease (PD) results from the degeneration of nigrostriatal dopaminergic neurons. This process ultimately leads to a progressive decrease in dopamine-mediated striatal signaling which manifests as a clinical syndrome characterized by bradykinesia, rigidity, tremor, and gait abnormalities. Traditional therapy for PD has aimed at restoring dopamine levels in the striatum through administration of the dopamine precursor, L-dopa. With advanced disease, L-dopa leads to dyskinesias and periods of marked fluctuation in motor activity ('on-off effect'). Alleviation of these side effects has been a major challenge and has prompted a search for alternative strategies which can provide a more stable level of dopaminergic signaling. A previously unexplored option to restore striatal dopaminergic activity and at the same time to potentially avoid the consequences of long-term L-dopa administration, is through the introduction of constitutively active dopamine receptors. The laboratory of the PI has extensive experience in generating receptors with ligand-independent (or constitutive) activity through the introduction of activating point mutations. These receptors have the potential to maintain dopaminergic signaling even in the absence of dopamine and/or dopaminergic agonist drugs. The premise of this application is that constitutively active dopamine receptors can be identified using *in vitro* assays and expressed in the striatum of rats to enhance dopaminergic signaling over an extended time interval. The objective of Specific Aim 1 is to generate and pharmacologically characterize *in vitro* a series of constitutively active dopamine 1 and dopamine 2 receptors. Using recombinant adeno-associated virus, the functional consequences of striatal overexpression of constitutively active dopamine receptors will be explored in rats (Specific Aim 2). Circling behavior after unilateral viral administration will be used as an index of construct activity. The methodologies utilized will include molecular (generation of constitutively active mutant receptors, expression of recombinant proteins), pharmacologic (radioligand binding, second messenger signaling assays), and behavioral approaches (assessment of circling behavior). These experiments will provide additional insight into the role of dopaminergic receptors in the striatum as well as potentially take the first steps toward the development of a new therapeutic option for Parkinson's disease. -

Principal Investigator: KRIEGSTEIN, ARNOLD R.

Grant Number: 5R13NS020032-21

Title: Neurobiology of Disease -- Teaching Workshop

Abstract: The Society for Neuroscience (SFN) is the major professional organization for scientists who study the nervous system. An important goal of this organization is to encourage scientists in training to undertake research related to diseases of the nervous system. The objective of this grant application is to support teaching workshops that introduce young neuroscientists to current concepts about the etiology and pathogenesis of disorders of the nervous system. For each workshop, about 12 faculty are chosen by the Organizing Committee after eliciting proposals from the Society at large. Clinical presentations provide enrollees with an experience of the human dimension of particular diseases. Lectures cover both clinical research and relevant laboratory work. In addition to lectures, enrollees are given a choice of attending two of four small group workshops that emphasize either specific or methodological issues and encourage lively discussion. Since its inception, 20 workshops have been held, usually on the day prior to the start of the Society for Neuroscience meeting. Topics have included: Infections in the nervous system, epilepsy, Huntington's and Alzheimer's diseases, muscular dystrophy, multiple sclerosis, prion diseases, drug addiction, pain and affective disorders, stroke and excitotoxicity, neuromuscular diseases, amyotrophic lateral sclerosis, schizophrenia, migraine, mental retardation and developmental disorders, Tourette's syndrome and obsessive-compulsive disorder, and the neurobiology of brain tumors. Enrollment generally runs between 100 and 200 attendees. Most enrollees are graduate students or postdoctoral fellows. Current plans are to cover the following topics in the near future: Genes, free radicals, mitochondria and apoptosis in Parkinson's disease, AIDS dementia, peripheral neuropathy, pain, language disorders, and affective disorders. Other topics will be chosen depending on their potential interest to young neuroscientists, their impact on society and the quality of recent research related to that disease area. We are especially interested in covering diseases of the nervous system which are important clinically but which are in need of enhanced basic cellular and molecular understanding. Society members are encouraged to suggest topics in the SFN Newsletter. -

Principal Investigator: KURLAN, ROGER M

Grant Number: 1U01NS050095-01

Title: Parkinson's Disease Data Organizing Center

Abstract: In response to RFA-NS-NS-05-001, we propose to establish a Parkinson's Disease Data Organizing Center (PD-DOC) at the University of Rochester. In keeping with the RFA, the PD-DOC will: 1) establish, maintain and disseminate a shared, central and standardized longitudinal database in support of the prospective collection and analysis of clinical, neuropathological and biologic data from patients with PD and controls, 2) assess and move toward the potential integration of relevant pre-existing databases, 3) assist investigators planning to perform research studies using the shared database, 4) prepare and maintain an up-to-date catalog of research materials at participating sites that might be used for PD research and, 5) coordinate annual meetings of the PD-DOC Steering Committee. The University of Rochester has extensive expertise and resources which will facilitate the development of a highly successful PD-DOC. The PD-DOC will be a critical force in advancing collaborative research in PD. -

Principal Investigator: LANGE, NICHOLAS T

Grant Number: 2R01NS037483-06A1

Title: Biostatistical Methods for Human Brain Mapping

Abstract: This is a continuing proposal to address a variety of biostatistical problems motivated by current issues in imaging neuroscience, as during the previous funding cycle. New aims: the development of flexible semiparametric growth curve models for accelerated longitudinal designs; advancing methodology for replicated spatial point processes and 3-D brain cell assemblies; and new methods and algorithms for semiautomatic identification of human brain cells. We propose to generalize our proposed individual low-rank smooth regression methods to compositional data via a logit-Gaussian model within a hierarchical Bayes framework. We seek to produce practical guidelines for designing cost-effective longitudinal studies involving expensive outcomes measurements. We propose to advance Poisson random field methods for sparse processes, motivated by the multiple cell types and regional structures in the human brain. Empirical data analysis will continue to play a central role in the proposed research. Our human brain mapping research by magnetic resonance imaging (MRI) and positron emission tomography (PET) and human brain tissue microscopy again relates directly to the study of psychiatric and neurological outcomes in healthy and ill subjects, both young and old. Through our collaborating biostatistical and neuroscience institutions, our ongoing translational research develops and links modern biostatistical methods with complementary work in longitudinal anatomic human brain imaging, functional human brain imaging and human brain tissue microscopy. Brain diseases addressed are schizophrenia, bipolar disorder and Parkinson's disease. However, potential applications of our methods go well beyond human brain mapping to include longitudinal and spatial epidemiology, risk assessment, health policy and management, nutrition, and other fields in which cost and feasibility constraints impose restrictions on the numbers of subjects studied and on the numbers and timings of their repeated measurements.-

Principal Investigator: LAU, YUEN-SUM

Grant Number: 5R01NS047920-02

Title: Impact of Exercise on Parkinson's Disease Therapy

Abstract: Parkinson's disease (PD) is a slow, progressive, debilitating, neurodegenerative disease, which has no cure. The current pharmacological therapies only temporarily mask symptoms, but do not protect neurons from further degeneration. Furthermore, chemotherapeutic agents often cause severe adverse effects and reduce the effectiveness of treatment. Numerous clinical reports have suggested that endurance exercise can slow down disease progression, and add years of independent and quality life to PD patients, or even improve the delivery and efficacy of L-DOPA treatment. Exercise therapy, or in conjunction with drug therapy at early onset of disease state, have been highly advocated by recent clinical trials. The potential health benefit and neurological mechanisms of action for exercise on PD rehabilitation have not been rigorously tested in the laboratory animal models. This research is designed to elucidate the impact of endurance exercise training on nigrostriatal dopamine (DA) neuron plasticity using a slow, progressive, and neurodegenerative mouse model of PD developed and characterized by our laboratory. This model is established based on a regimen of chronic 1-Methyl-4-phenyl - 1,2,3,6-tetrahydropyridine (MPTP) injections co-administered with probenecid, a drug that inhibits the peripheral and neuronal clearance of MPTP and potentiates the neurotoxicity of MPTP. In this model, we observed a marked decrease of nigrostriatal DA function within one week after treatment and remained low for 6 months. The animal also shows a gradual loss of substantia nigra (SN) neurons, decline of motor activity, and an accumulation of c-synuclein-immunoreactive inclusions in the SN. We further present in the application our preliminary findings supporting the feasibility and potential neuromodulatory role of endurance exercise on enhancing nigrostriatal DA transmission and PD rehabilitation using this model. In this research, we will test the following hypotheses centered on the endurance exercise, when administered at an early stage in the parkinsonian (PK) mice, will 1) improve their mobility and physical rehabilitation, 2) improve the efficacy of L-DOPA, 3) produce these effects by mechanistically causing an elevation of BDNF expression, an increase in the differentiation of DA progenitor cells, and an enhanced DA transmission and plasticity in the nigrostriatal neurons. Findings from this research should provide new insight into the development of alternative therapeutic approaches for enhancing the conventional pharmacological treatment and rehabilitation of PD. Potential benefits for using such a synergistic approach in managing PD would likely reduce the risk of drug toxicity and lower the cost of health

Principal Investigator: Munzar, Patrik

Grant Number: 2R44NS045505-02

Title: Inhaled dopamine agonists for late stage Parkinsonism

Abstract: Many patients in the later stages of Parkinson's disease experience periods of acute immobility ("off" periods) that substantially decrease their quality of life. The most effective pharmacological treatments for these acute "off" periods are dopamine agonist drugs, which can rapidly abort "off" periods if delivered quickly into the blood stream via injection. The utility of this form of treatment is, however, limited due to its invasiveness and the inability of many late-stage Parkinson's disease patients to self-administer injections. The aim of this project is to develop an inhalation device that delivers dopamine agonists rapidly into the blood stream in a convenient, non-invasive fashion. We have developed a novel drug delivery technology that involves heating drugs such that they vaporize, but do not degrade, and subsequently cool and condense into small particle aerosols suitable for systemic delivery by inhalation. In Phase I of this proposal, we have constructed a handheld device capable of generating pure aerosols of several dopamine agonists, demonstrated the biological activity of these aerosols in vitro, and confirmed that the aerosol's particle size is appropriate for systemic delivery via deep lung inhalation. In Phase II of this grant we will prove that inhaled dopamine agonists rapidly reverse Parkinson's disease symptoms in an animal model and will conduct all pre-clinical work required to initiate clinical development of inhaled dopamine agonist for treatment of late stage Parkinson's disease. Successful completion of these aims will allow us to move into Phase I clinical testing, which will be funded by a combination of outside investors, FDA funds for the development of orphan drugs, and/or a partnership with a major pharmaceutical company. Eventual FDA approval of inhaled dopamine agonist product for treatment of motor fluctuations in late stage Parkinson's will substantially improve the treatment of this serious and common neurodegenerative disease. -

Principal Investigator: OKUN, MICHAEL S

Grant Number: 5K23NS044997-02

Title: DBS Effects on Mood and Cognition in Parkinsons Disease

Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus interna (GPi) has been demonstrated to be effective in the treatment of the cardinal motor symptoms of Parkinson's disease (PD) (tremor, rigidity, and bradykinesia). Both STN and GPi DBS have been documented to be effective in treating parkinsonian motor signs. Due to early limited reports, which suggest more robust improvements in UPDRS motor scores, and the ability to reduce parkinsonian medication with STN, but not GPi, STN has been the preferred target of most centers. There is, however, increasing evidence that STN DBS may be associated with a significant number of mood and cognitive changes. Because of the small size of the STN (158mm³), stimulation within the sensori-motor area can result in spread to limbic and associative areas of STN as well as to surrounding structures and fiber systems that may also affect mood and cognition. Since the GPi (478mm³) is significantly larger than STN, a lead can be placed in the sensorimotor territory of the GPi with less likelihood of current spread to non-motor portions of the GPi or to adjacent structures and fiber systems that can adversely change mood and cognition. In this proposal we will 1) Characterize and compare the mood and cognitive changes associated with STN and GPi DBS, 2) delineate regions within or around the STN and GPi that are associated with specific mood and cognitive changes during DBS in these regions, and 3) assess the relative effect of right versus left STN or GPi stimulation on mood and cognition. This study will characterize the types and incidence of mood and cognitive changes that occur during stimulation in STN and GPi. It will also compare the relative changes in mood and cognition that occur in each site and examine the role of lead location in mediating them. The research is part of a five-year plan for training and career development for the Principal Investigator. This proposal includes active and experienced mentoring, access to diverse resources, and a scientific environment suited specifically for the development of the PI as an independent physician scientist.-

Principal Investigator: QUIK, MARYKA

Grant Number: 1R01NS047162-01

Title: Nicotinic and neuroprotection in a parkinson mouse model

Abstract: Our goal is to understand the effects of nigrostriatal damage and nicotine treatment on nicotinic receptor (nAChR) subtypes in the basal ganglia, and determine the relationship of any changes to neuroprotection. The rationale for such work is based, in part, on epidemiological studies showing that there is a decreased incidence of Parkinson's disease (PD) in smokers. This apparent neuroprotection may be due to nicotine in tobacco since nicotine protects against nigrostriatal damage in various experimental models. Nicotine exerts its effects by stimulating nAChRs. We hypothesize that nicotine-mediated protection against nigrostriatal damage occurs as a consequence of changes in nAChR subtypes. Our preliminary data show that there are differential changes in nAChRs subtypes and their function after MPTP treatment. In this proposal, we will test the effects of nicotine to modulate nAChRs, study its neuroprotective effects against nigrostriatal degeneration and investigate its mechanism(s) of action. This will be approached through the following Specific Aims. (1) We will test the hypothesis that nicotine administration influences nAChR expression and function in MPTP-treated mice. Although nicotine exposure is well-known to upregulate nAChRs in control animals, studies to determine its effects after nigrostriatal damage remain to be done. Next (2) we will test the hypothesis that nicotine-induced changes in nAChRs correlate with neuroprotection against nigrostriatal damage by measuring various markers of striatal dopaminergic function. These data will be correlated to changes in nAChRs to determine whether receptor alterations are linked to neuroprotection. (3) To determine whether specific nicotinic receptor subtypes are involved we will study whether nicotine protects against nigrostriatal damage in nAChR knockout mice. (4) Finally, experiments will be done to study the molecular mechanisms that mediate nicotine-induced neuroprotection. We will investigate the hypothesis that trophic factors such as basic fibroblast growth factor (bFGF) and brain derived neurotrophic factor (BDNF), as well as immune mediators such as interleukin-6, are involved. These studies will enhance our knowledge of the changes in nAChR expression and function with chronic nigrostriatal damage and nicotine treatment. This may allow for the design of neuroprotective strategies for PD, a disorder for which only symptomatic treatment is currently available.-

Principal Investigator: RACETTE, BRAD A

Grant Number: 5K23NS043351-03

Title: GENETICS OF PARKINSON DISEASE IN THE AMISH

Abstract: The applicant is a neurologist and movement disorders specialist with three years of post-fellowship, faculty experience involving clinical care, clinical trials, and clinical research into etiologic risk factors for PD including genetic factors. The goal of this career development award is to provide the applicant with comprehensive training in genetic epidemiology through course work, individual tutorials, and practical application of gene mapping techniques to a multi-incident Amish family with Parkinson Disease (PD). PD is a neurodegenerative disorder that produces substantial disability for nearly 1 million people in North America. There is no known cause of the disease in the majority of patients; however, a genetic etiology has been found in a few rare multi-incidence families. Identification of such genes and subsequent determination of the cell biological effects of these mutations will provide important clues to the pathophysiology. Each new mutation discovered adds critical converging evidence about pathophysiological mechanisms common to all to those affected with PD. We have identified 27 members of a large Amish family with clinically typical PD and have excluded known PD genetic mutations. However, we still need to prove that PD is inherited in this pedigree. We will use two different methods to prove that PD in this kindred has a genetic basis. The first approach will assume an autosomal recessive model of inheritance and use genetic marker data provided by CIDR on our subjects to perform homozygosity mapping. A second approach will be to calculate a kinship coefficient to determine if the affected members of the pedigree are "more related" than randomly selected age-matched individuals from the same population. Finally, we will test whether [18]FDOPA PET permits the conversion of some people identified clinically as possible or probable PD in to PET-confirmed PD and thereby functioning as an endophenotype for disease state. This family provides a unique opportunity for the candidate to become a productive independent investigator in genetics of Parkinson Disease and other movements disorders and to develop skills needed for interpretation of [18]FDOPA PET.-

Principal Investigator: RICHARD, IRENE H
Grant Number: 5K23NS002184-05
Title: MOOD FLUCTUATIONS IN PARKINSON'S DISEASE

Abstract: The candidate has a clinical background in neurology with an expertise in movement disorders and has completed a two year NIH-funded fellowship through the Department of Neurology in Experimental Therapeutics. This fellowship provided the candidate with both theoretical knowledge and practical experience pertaining to the design and conduct of clinical trials. She has focussed most of her efforts thus far on the understanding and treatment of the behavioral aspects of Parkinson's disease (PD). The candidate's short term goals include the following: 1) to increase her knowledge of basic pharmacology and gain experience using techniques relevant to pharmacologic mechanism oriented research, 2) to gain a better understanding of molecular medicine, 3) to obtain training in psychiatric assessment techniques, 4) to expand her knowledge of areas fundamental to clinical investigation including biostatistics, epidemiology and outcomes research. The focus of her research plan during this career development award will be understanding mood fluctuations in PD. Mood fluctuations have been reported in up to 2/3 of advanced PD patients who experience motor fluctuations. These can be frequent, dramatic and distressing. Research involving the phenomenology and underlying mechanisms of mood fluctuations in PD has been limited. The specific aims of this study are to: 1) better understand the phenomenology of mood fluctuations in PD (frequency, quality, magnitude), 2) better understand the relationship between mood fluctuations and more pervasive depressive disorders in PD, 3) clarify the temporal relationship between changes in mood and motor states in PD, 4) elucidate the neurobiological mechanisms of changing mood states in PD and to determine, in particular, whether mood fluctuations in PD are the result of dopamine dysregulation, and 5) gather preliminary information regarding the optimal treatment of mood disorders in PD. These findings may lead to the development of therapeutic interventions for patients with PD who suffer from these disabling fluctuations on a daily basis. It may also provide a better understanding of the mechanisms responsible for more pervasive forms of depression in PD, and perhaps even in primary psychiatric mood disturbances. -

Principal Investigator: SAUNDERS-PULLMAN,
Grant Number: 1K23NS047256-01
Title: Gender and Hormonal Differences in Parkinson's Disease

Abstract: This application is directed to the career development of Dr. Rachel Saunders-Pullman as a clinical researcher in the study of hormonal effects on Parkinson's Disease and other neurodegenerative disorders. During the period of this grant she will focus on gender differences and the role of hormones in the development of Parkinson's disease (PD). As hormone physiology is complex, and estrogenic compounds can be carcinogenic as well as beneficial, the assessment of the role of estrogen and gender differences and the planning of clinical trials requires multi-disciplinary knowledge and training. The candidate has constructed a training program with areas of emphasis in epidemiology, neuroscience and neuroendocrinology, cognition and movement disorders using an integrated plan of research, coursework, lectures, and rounds. Her primary sponsor, Dr. Richard Lipton will oversee the methods and the candidate's development in epidemiology and cognition as well as the overall training. The co-sponsor, Dr. Susan Bressman will provide guidance in the field of movement disorders. A consultant team of Dr. Anne Etgen, Dr. Nanette Santoro and Dr. Charles Hall will complement with expertise in neuroscience and neuroendocrinology and biostatistics, respectively. In order to address gender related differences in risk of PD and clinical features of PD, and whether hormonal factors account for these differences, three separate studies with differing study designs are proposed. These studies were designed to provide complementary answers to specific research questions and to give the candidate hands-on, mentored exposure to three major types of epidemiologic research 1) a clinic-based prospective study of gender differences in the natural history and disease course in early PD, 2) a case-control study of pharmacy records to assess whether exogenous estrogen decreases the risk of PD and 3) a cross-sectional and a prospective evaluation of the role of gender and endogenous hormone levels on motor control measures in aging and pre-clinical parkinsonism in an established cohort study. Through the aggregate of the training program and supervised research, the candidate will emerge as an independent researcher well prepared to answer questions of the role of hormones in neurodegenerative diseases and movement disorders. -

Principal Investigator: SMITH, AMANDA D

Grant Number: 1K01NS045698-01A1

Title: Endogenous neuroprotective agents in Parkinson's disease

Abstract: The present application describes the research and career plan laid out for my development into an independent, productive, and well funded investigator in the area of the neurobiology of neurodegenerative disease. The research plan that is proposed investigates the role of circulating insulin like growth factor (IGF-1) and associated proteins in protection of the nigrostriatal dopamine (DA) pathway against oxidative stress induced by 6-hydroxydopamine (6-OHDA) and the nature of this protection. The loss of DA neurons in this pathway underlies the motor dysfunctions observed in patients with Parkinson's disease (PD). Forced use of the impaired forelimb for 7 days in a unilateral 6-OHDA lesion model of Parkinson's disease, ameliorates behavioral asymmetry and restores DA content in the striatum when commenced immediately after or prior to neurotoxic insult. The mechanism by which forced use protects against 6-OHDA toxicity is unknown. Moreover, whether forced use protects the nigrostriatal pathway from degenerating, rescue cells in danger of degenerating in the absence of intervention, or promotes sprouting, is not known. Physical exercise by treadmill or running wheel has been shown to increase the brain uptake of IGF-1 from the circulation and this IGF-1 has been shown to mediate exercise-induced increases in neurogenesis and brain derived neurotrophic factor mRNA in the hippocampus. Thus, it may be surmised that forced use protection is mediated via increases in brain IGF-1 subsequent to increases in circulating IGF-1. Our preliminary data using Fluoro-jade B as a marker of degeneration suggests that forced limb use prevents the nigrostriatal pathway from degenerating. Further, a preliminary screen of altered genes after 6-OHDA and 6-OHDA +/- forced limb use, with microarray analysis suggests that IGF-1 may be involved. In the present proposal, we will: 1) Further examine the impact of forced use/disuse on the anatomical and functional state of DA neurons using behavior, biochemistry and histological analyses; 2) investigate the role of IGF-1 in forced limb use-induced protection, whether this effect can be mimicked by systemic administration of IGF-1 and whether subsequent up-regulation of other trophic factor signaling (i.e. GDNF and BDNF) is involved; and 3) examine whether the protective effects of forced limb use and IGF-1 are mediated via activation of the pro-survival phosphatidylinositol 3-kinase (PI 3K)/Akt and extracellular signal-regulated kinase (ERK) signaling cascades. The career development plan in the present proposal focuses on providing me with the technical skills needed to accomplish the Aims outlined in the present proposal. Further, it will provide the skills and

Principal Investigator: SORTWELL, CARYL E

Grant Number: 1R13NS049951-01

Title: American Society for Neural Transplantation and Repair

Abstract: This R13 application seeks funding to support graduate student/postdoctoral fellow travel awards to the annual meeting of the American Society for Neural Transplantation and Repair (ASNTR). Since its founding in 1994, the ASNTR has convened yearly each April/May in Clearwater, Florida. At the meeting various research advances in the fields of transplantation and gene therapy applied to neurodegenerative diseases such as Parkinson's disease, Huntington's disease, Alzheimer's disease, stroke, spinal cord injury and traumatic brain injury are discussed via platform and poster presentations. Attendance of this meeting ranges between 150-250 registrants. Each year the ASNTR Education Committee encourages students/postdocs to submit their abstracts in a competition and the top rated students/postdocs receive travel awards to cover the cost of their meeting attendance and travel. ASNTR has always placed a high priority on funding travel awards for students and post-doctoral fellows presenting their scientific findings at the yearly conference. As the field of neural transplantation and repair continues to expand we feel that it is critical to support students and postdocs so that they may attend this meeting and share their recent scientific findings with leaders in their field of research. In the past ASNTR has received donations from biotech companies and non-profit organizations to cover these travel awards. However, in recent years ASNTR has seen these contributions dwindle and although ASNTR will continue to seek funding from the private sector, we do not anticipate any increase in contributions above recent levels in the coming years. This application requests \$15,000 in total direct costs to support travel awards for the top 15 graduate students/postdocs from US institutions that apply (awards of \$1000 per student/postdoc). -

Principal Investigator: SUN, GRACE Y

Grant Number: 1R13NS047414-01

Title: Conference on Oxidative Mechanisms in Neurodegeneration

Abstract: This application seeks funds for partial support of US investigators to attend a symposium entitled "Oxidative mechanisms in Neurodegenerative disorders" to be held in Guilin, China, August 9-13, 2003. The symposium is a satellite to the International Society of Neurochemistry/Asian Pacific Society of Neurochemistry (ISN/APSND) that will be held in Hong Kong, August 2-7. The Central Nervous System (CNS) is highly susceptible to oxidative stress, which alters many metabolic pathways leading to cellular dysfunction. Since increase in oxidative stress has been implicated in the pathophysiology of a number of age related neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease and stroke, this symposium brings together world-class scientists to share new findings and insights on oxidative mechanisms underlying these neurodegenerative disorders. In addition to sessions focused on oxidative mechanisms associated with Alzheimer's disease, Parkinson disease, stroke, and receptor signaling pathways, a special session will be dedicated to discussing novel methods for intervention and prevention. Thus, this symposium not only provides mechanisms for international scientists and young investigators to focus on an important topic of immense interest to neuroscientists, it also provides opportunities for investigators outside of China to learn and interact with Chinese investigators in basic and clinical aspects of neurodegenerative diseases. In addition, plans are in progress to provide rapid publication of the symposium proceedings in an internationally recognized neuroscience journal. -

Principal Investigator: TESTA, CLAUDIA M

Grant Number: 5K08NS044267-03

Title: Mitochondrial dysfunction in neurodegenerative disease

Abstract: Like most neurodegenerative disorders, Parkinson disease (PD) has a chronic, slowly progressive course, selective neuronal loss, and a small percentage of familial cases caused by mutations in widely expressed genes. A simplified, reproducible and relevant model system that allows study of progressive neuronal injury would permit us to examine mechanisms of chronic neurodegeneration in PD, and allow us to screen potential neuroprotective agents. Organotypic "slice" culture models offer major advantages in that they are simplified compared to in vivo models, yet unlike dissociated cell cultures they involve the use of mature neurons, remain viable in culture for months, and maintain substantial intact circuitry and neuronal-glial interactions. We propose to characterize and use such a model to specifically examine mechanisms of neuronal injury in PD. Mitochondrial dysfunction has been proposed as a factor underlying dopaminergic cell loss in PD. There is growing evidence of decreased mitochondrial function and increased oxidative stress in human PD. In a new animal model of PD, systemic infusion of the mitochondrial toxin rotenone, an organic pesticide, causes degeneration of the nigrostriatal pathway that is highly selective, even in the presence of global mitochondrial inhibition. In the current proposal we will: 1) Optimize and characterize a rotenone model of PD in chronic organotypic slice cultures. We present data from preliminary studies demonstrating the successful use of slices containing substantia nigra pars compacta dopaminergic neurons for this purpose. 2) Exploit the unique advantages of this system to investigate the mechanisms of action of mitochondrial inhibition. We will examine the role dopamine itself plays in neuronal vulnerability, and look for evidence of oxidative damage and apoptotic cell death. 3) Investigate the interaction of genetic defects with environmental stressors in PD. We will use transgenic mouse models to examine how rotenone interacts with genetic mutations that produce familial PD. We will study how underlying genetic lesions that affect oxidative stress and apoptosis pathways may predispose cells to damage from exogenous toxins. 4) Test potential neuroprotective agents in a model of chronic neurodegeneration that is highly relevant to PD. The research outlined above is part of a customized five-year plan of training and career development for the Principal Investigator. The proposal includes active mentoring by experienced scientists, access to diverse resources, and an environment uniquely suited to help the PI develop as an independent physician scientist.-

Principal Investigator: TROYER, MATTHEW D

Grant Number: 5K08NS002251-05

Title: OXIDATIVE STRESS/ALPHA-SYNUCLEIN IN PARKINSON'S DISEASE

Abstract: Parkinson's disease (PD), the second most common neurodegenerative disorder, results from selective loss of midbrain dopamine neurons. Both oxidative stress and intracellular aggregation of proteins, including the protein alpha-synuclein, are implicated in this degeneration. However, the source of oxidative stress, the mechanism of alpha-synuclein deposition, and the relationship between them are unknown. We will examine the role of the neurotransmitter dopamine in generating oxidative stress by manipulating its synthesis, degradation and vesicular transport and measuring production of reactive oxygen species. We will also investigate the effect of dopamine-mediated oxidative stress on alpha-synuclein deposition in model cell culture systems. We will then use this information to determine conditions that promote alpha-synuclein deposition in transgenic mice expressing wild type human alpha-synuclein or a mutant alpha-synuclein that causes an autosomal dominant form of PD. Thus we hope to identify factors that promote oxidative stress in dopamine neurons and to better understand the mechanisms and significance of alpha-synuclein deposition in PD. This work will be conducted under the sponsorship Dr. Robert Edwards in the Departments of Neurology and Physiology at UCSF. Through this work I will learn new techniques in molecular biology, biochemistry and imaging that I will continue to apply to PD. Dr. Edwards and I have developed a training program that includes laboratory research, coursework and didactics that will enable me over the next five years to become an independent investigator concentrating on the neurobiology of PD. In the long term I intend to spend 75% or more of my time dedicated to scientific investigation of PD, and to direct my clinical activities toward patients with PD and other movement disorders. -

Principal Investigator: UC, ERGUN Y

Grant Number: 5R01NS044930-02

Title: Predicting Driver Safety in Parkinson's Disease

Abstract: Automobile driving is a crucial aspect of everyday life, yet vehicular crashes pose a serious public health problem. Drivers with Parkinson's disease (PD) are at special risk for a crash due to progressive impairments of motor function, cognition, and daytime arousal. Some drivers with PD are especially likely to drive while impaired because they are not aware of performance impairments, and neither are their physicians. Judgments on fitness to drive in at-risk drivers with PD should rely upon empirical observations of performance, because decisions based on medical diagnosis or age alone may unfairly deny patients their mobility or unwisely authorize licensure in unfit drivers. We propose to expand the available knowledge of driving safety in PD by testing a set of hypotheses in experiments that will assess (1) motor function using standardized measures of parkinsonism, (2) cognitive functions using standardized neuropsychological tests (of attention, perception, memory, and executive functions), (3) daytime arousal (standard self-ratings of sleepiness and monitoring of lid closure), and (4) driving performance as measured in an instrumented vehicle and a state-of-the-art interactive driving simulator. Our pilot study of drivers with PD shows the feasibility of this approach. Simulators make it possible to observe driver errors with optimal stimulus and response control in an environment that is challenging yet safe for the driver and tester. Participants in this project will be 115 legally licensed drivers with PD and an equal number of control drivers without neurological disease. Allowing for attrition, 100 of these 115 drivers with PD will be re-tested two years after the initial driving assessment to measure effects of PD progression on driver safety. Our goal is to increase understanding of the role of PD-related motor dysfunction, cognitive impairment, and daytime arousal disorders in driving safety errors. A better understanding of how driving performance deteriorates in PD and whether drivers are even aware of their impairment is a necessary step in the rational development of interventions that could help prevent crashes by patients with PD. The techniques used in this study could ultimately be adapted to develop future tools for screening, identifying, advising, and alerting drivers with PD who are at greater risk for impaired driving. Fair and accurate means of detecting unfit drivers with PD will help mitigate the tragedy of motor vehicle crashes caused by these impaired individuals.-

Principal Investigator: York, Michele

Grant Number: 5K23NS041254-03

Title: Cognitive functioning following deep brain stimulation

Abstract: Dr. Michele York, under the mentorship of Dr. Harvey Levin, Director of Research of Baylor College of Medicine's (BCM) Physical Medicine and Rehabilitation Department and Professor of Psychiatry and Neurosurgery, and Dr. Robert Grossman, the Chairman of BCM's Neurosurgery Department, will more effectively evaluate the long-term cognitive effects of deep brain stimulation (DBS) for the treatment of Parkinson's disease (PD). The scientific objective of the proposed research plan is to more clearly understand the relationship between the frontostriatal neural circuitry affected by DBS and PD and cognitive functioning. The clinical objectives of the proposed research plan include improving upon the evaluation of outcome by improving cognitive diagnostic techniques, clarifying the clinical criteria for surgical selection, and incorporating analysis of post-operative magnetic resonance imaging (MRI) findings. To achieve these aims, Dr. York will compare the executive functioning of patients undergoing staged bilateral subthalamic (STN) and globus pallidus (GPI) DEIS to patients who receive the best medical management for the treatment of PD on verbal fluency measures administered under conditions of set shifting and attentional control and working memory measures, which are cognitive processes dependent on the functional integrity of frontostriatal circuitry. The relationship between DBS electrode placement and performance on these frontostriatal neuropsychological tasks will also be investigated. The objectives of the training program are to acquire practical and technical skills that will aid Dr. York in developing her career, specifically in the areas of neurosurgical interventions and neurological evaluations of PD, structural and functional neuroimaging, and the neuroscience of PD. This training will provide Dr. York with a better understanding of the cognitive deficits in PD and the mechanisms and consequences of emerging interventions for the treatment of this neurological disease. The training activities during the award period will consist of 3 major components: 1) Didactics through coursework, technical training seminars, rounds, and observation, 2) Supervisory Guidance through regularly scheduled meetings with mentors and an Advisory Committee, and 3) Instruction in the Responsible Conduct of Research. Dr. York will gain the necessary knowledge to attain her long-term career goal of working as an independent clinical researcher by acquiring the background and skills in neuroscience, neuroimaging, and grant preparation needed to write a ROI proposal to adapt these cognitive tasks to a functional imaging setting to further elucidate the neural mechanisms of PD and DBS. -

Principal Investigator: ZABETIAN, CYRUS P

Grant Number: 5K08NS044138-03

Title: DBH as a Modifying Gene in Neurodegenerative Diseases

Abstract: The applicant, Dr. Cyrus Zabetian, has spent the past three years as a postdoctoral fellow at Yale University/VACHS. He will join the neurology faculty at the University of Washington next year where his future mentors, Drs. Thomas Bird and Gerard Schellenberg, have established a superb research program in neurogenetics. His training will include participation in laboratory meetings, seminars, structured courses, and annual scientific meetings. He will become part of a rich collaborative network of researchers with expertise in clinical and molecular neurogenetics, catecholamine biochemistry, and biostatistics. Dr. Zabetian's long-term plans are to become established as an independent laboratory investigator within five years, and remain actively involved in patient care and resident training on the neurology service. In neurodegenerative disease research, identifying genetic mechanisms underlying compensatory changes in surviving neurons promises to lead to improved strategies of diagnosis and treatment. The project proposed in this application seeks to determine if a newly discovered promoter polymorphism (C-1021T) influences regulation of the DBH gene with potential clinical consequences in Parkinson's disease (PD), and is divided into three parts. The goal of part I is to evaluate whether homozygosity for the T allele of C-1021 T, which is associated with low levels of plasma DBH enzyme, is predictive of an earlier onset and more severe symptoms of sympathetic failure in patients with PD. A group of forty subjects homozygous for either the C or T allele will be selected from a population of 400 clinic patients with PD and assessed longitudinally using indices of sympathetic function. Part II seeks to determine whether C-1021T strongly associates with DBH expression in noradrenergic tissues. Levels of DBH protein and mRNA will be compared in postmortem human adrenal medulla specimens, homozygous for either the C or T allele, using western blots and quantitative real time RT-PCR, respectively. Part III will assess whether C-1021T is directly functional. If preliminary results are favorable, two transgenic mouse lines homozygous for either the T or C allele will be created in which the proximal 2 kb of the endogenous mouse DBH promoter is replaced by homologous human sequence. Comparing plasma and tissue levels of DBH protein and catecholamines in the two lines will detect the effect of each allele on DBH expression.-

Principal Investigator: ZIGMOND, MICHAEL J

Grant Number: 5T32NS007391-08

Title: Training in the Neurobiology of Neurodegenerative Disease

Abstract: We request continuing support for this postdoctoral training program in basic neuroscience as it relates to neurodegenerative disease and stroke. The program is closely integrated with several key research programs related to Parkinson's disease, Alzheimer's disease, ALS, and stroke. Additional programs in psychiatric disorders and in neuroAIDS further enhance the environment. The grant will permit us to maintain the critical mass needed to recruit the best possible postdoctoral trainees, including under represented minority trainees, and to offer a training program of the highest quality. Our training program focuses primarily on basic and translational laboratory research that can readily be related to neurodegenerative disease and stroke. The major research advisor and an individualized research advisory committee, a professional development committee, and the training grant steering committee share the task of guiding and monitoring each trainee. All trainees participate in three activities which supplement their research experience: (1) Two seminars on the neurobiology of clinical disorders, (2) a monthly research discussion, and (3) a series of professional development workshops. Issues of responsible conduct are integrated into the entire program. Trainees also participate in courses as needed and have opportunities to teach and to observe clinical practice. The 39 members of the training faculty are members of the university-wide program in neuroscience with a particular interest in neurodegenerative disorders and stroke. Most of the faculty members have extensive experience in training and in research and have significant grant support. In addition, we have included a small group of junior faculty who have outstanding promise and will be available to serve as co-mentors in conjunction with a more senior faculty member. At present our training faculty supervise more than 90 postdoctoral trainees (in addition to a large number of predoctoral students), of whom about 20 are eligible for NRSA support. We are requesting stipends to support an initial complement of 4 postdoctoral trainees, increasing gradually to 8 over a 5-year period. We believe that our training program provides an opportunity for outstanding postdoctoral trainees to prepare for a career of direct relevance to issues of neurodegenerative disease and stroke. -